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EXAMINER	
TUCKER, ZACHARY C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,279	MARTIN, THOMAS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

As requested in the correspondence filed 1 July 2004, which is in reply to the Office action mailed 26 April 2004, claims 1-10 have been cancelled, and new claims 11-22 have been added.

Status of Previous Claim Rejections - 35 USC § 112

In the previous Office action, mailed 26 April 2004, claim 10 was rejected under the first paragraph of 35 U.S.C. 112, for failing to comply with the enablement requirement.

Claim 10 has been cancelled.

New claims 15, 16, 21 and 22 correspond to the previously presented method claims, and the previously stated rejection of claim 10 for failing to comply with the enablement requirement is now applied to new claims 15, 16, 21 and 22.

Claims 15, 16, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Wands factors provide a guide for determining whether or not the enablement requirement under 35 U.S.C. 112, first paragraph, has been met:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.
In re Wands, 858 F.2d 731,737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Claims 15, 16, 21 and 22 are drawn to a method of treating bronchitis, allergic bronchitis, asthma, bronchial asthma, COPD, allergic conjunctivitis, allergic rhinitis, arthritis, rheumatoid arthritis, periodontitis, anaphylaxis, interstitial cystitis, dermatitis, sclerodermatitis, Crohn's disease and inflammatory bowel disease comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Though applicants have limited the number of disorders considerably, replacing the extremely broad "airway disorder" with the list above, the number and types of conditions embraced by the language of claims 15, 16, 21 and 22 remains quite broad. Some of the conditions, like bronchitis, allergic bronchitis and rheumatoid arthritis, are distinct medical conditions, but others are nebulous, like "COPD," arthritis and dermatitis. COPD, as was stated previously in reference to the broad recitation "airway disorder," reads on conditions bearing no relation to the tryptase, such as emphysema caused by tobacco smoking, which is the result of corruption of alveolar tissue integrity. Dermatitis is caused by innumerable factors, and 'arthritis' embraces any inflammation of the joints, which is a common characteristic of many diseases.

The crux of the rejection is maintained, that the specification does not enable one of ordinary skill in the art (at the time the invention was made) to treat *any* disease or condition with a compound according to the invention.

(B) The invention according to instant claim 10 is medical.

(C),(D) As evidence of the state of the art with respect to instant claim 10, the following reference is presented:

Burgess, "Mast Cell Tryptase as a Target for Drug Design" Drug News Perspectives, vol. 13(3), pages 147-157 (April 2000).

Chemical compounds having the property of inhibiting the enzymes known as tryptases, as the instantly claimed compounds allegedly posses, were known at the time the invention was made. The prior art acknowledges that such agents hold promise in development of treatments for certain diseases.

Burgess summarizes the state of the art at the time the invention was made, and exemplifies the extent of the knowledge held by one of ordinary skill in the art, in this case, a medical doctor specializing in treatment of airway disorders, about tryptase inhibitors and their application in medicine.

The conclusion reached by Burgess, after a discussion of the current state of the art is simple – that tryptase inhibitors hold promise as therapeutic agents, but no methodology of treating *any* disease with a tryptase inhibitor had heretofore been developed (page 155). It is not known whether inhibition of tryptase would have an effect on the course of any particular disease, only that elevated levels of mast cells and/or released tryptase is associated with several human diseases like asthma, rheumatoid arthritis, osteoarthritis, allergic conjunctivitis, allergic rhinitis, unstable angina, atherosclerosis, psoriasis and multiple sclerosis (page 148).

The following new reference is now presented to further elaborate on the dearth of know-how available to one of ordinary skill in the art relating to treatment of diseases with compounds that have the property of inhibiting tryptases.

Wright et al, "Inhibition of Allergen-Induced Pulmonary Responses by the Selective Tryptase Inhibitor 1,5-bis-{4-[(3-Carbamidoyl-benzenesulfonylamino)-methyl]-phenoxy}-pentane (AMG-126737)" Biochemical Pharmacology, vol. 58, pages 1989-1996 (1999).

Wright et al focuses on a compound similar to those which are instantly claimed, the type of compounds that Burgess denotes "bifunctional inhibitors" (page 152 of Burgess).

Wright et al discloses some experiments with the compound dubbed AMG-126737 on guinea pigs and sheep. Although the compound was able to attenuate antigen-induced hyperresponsiveness in the animals, the conclusion reached by Wright et al is as follows:

It is important to consider whether inhibition of tryptase alone is sufficient to provide effective therapeutic intervention in asthma. Other serine proteases have been reported to contribute to airway responses associated with asthma. Leukocyte and tissue-derived serine proteases also are elevated in the airways of asthmatic patients [3, 4, 37]. In addition, such proteases, including cathepsin G [38, 39], elastase [39–41], and tissue kallikrein [37], have been implicated in promoting physiologic responses associated with asthma as well as chronic airway remodeling associated with this disorder. It should be noted that tryptase inhibition can prevent increases of leukocyte protease levels indirectly by preventing leukocyte infiltration into the airways [6, 15]. Like tissue kallikrein, tryptase also has been shown to contribute to the generation of bronchoactive kinins [10]. However, the effect of tryptase inhibition on the protease tone of asthmatic airways remains to be characterized.

It is increasingly recognized that effective asthma therapy should prevent pathophysiologic airway responses such as recurrent bronchoconstriction and development of airway hyperresponsiveness as well as chronic pathologic changes of the asthmatic airway [42]. While its mechanistic roles have not been elucidated fully, tryptase appears to have an effector function in both asthma symptomatology and pathology. This and other reports [6] support the role of tryptase in antigen-induced effects on airway mechanics. The ability of tryptase to potentiate mast cell and leukocyte activation as well as smooth muscle responsiveness suggests that the enzyme is a key contributor to overall reactivity of the asthmatic airway. In addition, its mitogenic effects on fibroblasts and smooth muscle cells suggest that tryptase has a direct role in airway remodeling. Evaluation of the ability of tryptase inhibitors such as AMG-126737 to prevent chronic airway pathology is critical to fully assess the therapeutic potential of tryptase inhibition in asthma.

These statements clearly demonstrate that treatment of no disease was within the level of an ordinary physician's skill in 1999, when the instant application was filed.

(E) Burgess addresses the level of predictability with respect to the activity of tryptase inhibitors on page 148. If a compound demonstrates *in vitro* activity as a tryptase inhibitor, this is not predictive of the overall effect that such a compound would have on any particular disease in an animal, and also that activity in one animal does not predict activity in another animal, due to the "profound differences in substrate specificity, tissue distribution, stabilization requirements and regulatory mechanisms for mast cell tryptases across these various species (including human)..."

(F) Page 46 of the instant specification describes ways in which the active compounds of the invention can be administered in the treatment of respiratory disorders. Inhalation of a micronized powder is taught as the preferred mode of administering compounds of the invention in the treatment of respiratory disorders. Though page 46 teaches a dosage ranging from 0.1-10mg/Kg per day if the active compound is administered *p.o.* or IV, no dosage range is provided for administering compounds of the invention by inhalation.

(G) *In vitro* IC_{50}'s are reported on page 48 of the instant specification for 15 of the compounds according to the invention are the extent of the working examples.

(H) A medical doctor would not be capable of developing a method of treatment commensurate in scope with the method according to instant claims 15, 16, 21 and 22, given his level of skill and the guidance provided in the instant specification, without an undue amount of experimentation.

Practicing physicians do not routinely carry out investigations such as the ones described in Wright et al and Burgess. Even if this were not so, the amount of guidance in the specification merely suggests that the methods as claimed *might be* possible, leaving one of ordinary skill in the art to figure out for himself whether such methods are in fact medically feasible.

In the previous Office action, claims 1-10 were rejected under 35 U.S.C. 112, second paragraph, for indefiniteness. The rejection and accompanying explanations are found at pages 6-9 of the Office action mailed 26 April 2004.

Since claims 1-10 have been cancelled, the rejection is moot. Applicants have corrected the deficiencies under 35 U.S.C. 112, second paragraph, which were raised in the previous Office action.

Status of Claim Rejections - 35 USC § 102

In the previous Office action, mailed 26 April 2004, claims 1 and 2 were rejected as being anticipated by Rødbotten et al, "Stereoselective Synthesis of Alkynylglycines and α,α'-Alkynyl-Bridged Bis(glycines)" Acta Chemica Scandinavica, vol. 51, pages 873-880 (1997).

As claims 1 and 2 have been cancelled, the previously stated rejected is moot.

New claims 11-22 do not read on Rødbotten et al's α,α'-alkynyl-bridged bis(glycines), by virtue of the clarification of the manner in which bonds between the terminal nitrogen atom as defined in K2 and the same in K1 are counted.

On the direct route along the bonds between its terminal nitrogen atoms, Rødbotten et al's compounds have less than 20 bonds, when counted as defined in new claim 11.

In the previous Office action, mailed 26 April 2004, claims 1 and 2 were rejected as being anticipated by Crisp et al, "Elaboration of the Side-Chain of Amino Acid

Derivatives by Palladium Catalysed Couplings" Tetrahedron, vol. 53(51), pages 17489-17500 (1997).

As claims 1 and 2 have been cancelled, the previously stated rejected is moot.

New claims 11-22 do not read on Crisp et al's compound **2**, on page 17491, which was the basis for the rejection. On the direct route along the bonds between its terminal nitrogen atoms, this compound has less than 20 bonds, when counted as defined in new claim 11.

Response to Argument

Applicants' argument in response to the finding of lack of enablement which was set forth in the previous Office action mailed 26 April 2004 is as follows:

> The specific diseases listed in claims 15-16 and 21-22 have basis in the specification at page 45. As a result, one of ordinary skill in the art would be properly enabled to make and/or use the invention as presently claimed.

Merely reciting diseases in the specification does not provide enablement. The argument is unpersuasive.

New Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon review of the application, the following new claim rejection is seen as necessary –

Claims 11-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts, hydrates, and salts of hydrates of the claimed compounds, does not reasonably provide enablement for making solvates in general (solvates with all solvents) of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

b) Direction provided by the specification to one of ordinary skill in the art, as guidance for preparation of solvates, and therefore the guidance necessary for the preparation of salts of solvates of the instantly claimed compounds is found at page 7 of the instant specification where the following statement appears:

> It is known to the person skilled in the art that the compounds according to the invention, and also their salts, may contain varying amounts of solvents, for example when they are isolated in crystalline form. The invention therefore also embraces all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

A solvate is not merely a crystallized sample which still contains some solvent. Rather, a solvate is a distinct crystalline form with solvent molecules incorporated into the crystal lattice in an ordered fashion, in specific, stoichiometric amounts. The direction in the specification does not inform one of ordinary skill how to prepare a solvate of a compound according to the invention.

c) There is no working example of any solvate formed. The claims are drawn to solvates, yet the numerous examples wherein the product is crystallized from dichloromethane all failed to produce a dichloromethane solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic

molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, *i.e.* if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate.

h) The breadth of the claims includes all of the thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term "solvate". All conceivable solvents are contemplated by the recitation of "solvates" generally. Thus, the scope is quite broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or

use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

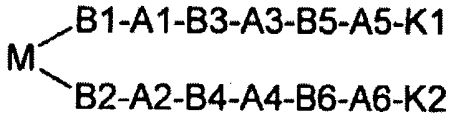
All claims 11-22, whether they be drawn to compounds, compositions or methods of treatment, are included in this rejection under 35 U.S.C. 112, first paragraph, because all claims include solvates and solvates of salts of the compounds according to formula (I).

Specification

As the abstract, applicants have supplied the abstract published with this application's WIPO publication.

The abstract of the disclosure is objected to because structural variables M, B1, B2, B3, B4, B5, B6, A1, A2, A3, A4, A5, A6, K1 and K2 are referred to, along with the statement "have the meanings indicated in the description," yet not structural formula of (I) is shown in the abstract. Thus, the abstract does not actually describe the invention.

A new abstract with the structural formula (I):



is recommended.

Correction is required. See MPEP § 608.01(b).

Allowable Subject Matter

Claims 11-14 and 17-20 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, first paragraph, set forth in this Office action.

Deletion of "a solvate" and "or a solvate of a salt thereof" in all occurrences would render the new rejection under 35 U.S.C. 112, first paragraph moot.

Conclusion

This Office action is non-final due to the new rejection under 35 U.S.C. 112, first paragraph, for lack of enablement of preparation of the claimed solvates and salts of solvates. A review of the disclosure prompted the rejection, which could have been set forth previously.

Before issuing this action, the examiner made two attempts, on 19 and 23 August 2004, to contact applicant's counsel, with the intention of requesting authorization to make the changes necessary to place the application in condition for allowance. Although two voicemail messages were left for applicant's counsel, no return call was received.

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday-Friday from 6:30am to 3:00pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (571) 272-0674.

If, after a 24-hour period, Dr. Shah is unreachable, contact the examiner's acting supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-2717.

zt

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624